



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/334,969	06/17/1999	BENT KARSTEN JAKOBSEN	102286.410	5926
7590 10/13/2004				
HOLLIE L BAKER HALE AND DORR LLP 60 STATE STREET BOSTON, MA 02109			EXAMINER DIBRINO, MARIANNE NMN	
			ART UNIT 1644	PAPER NUMBER
DATE MAILED: 10/13/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/334,969

Applicant(s)

JAKOBSEN ET AL.

Examiner

DiBrino Marianne

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 June 2004 and 12 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11, 14-27 and 34-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11, 14-27 and 34-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/04 has been entered.

2. Applicant's amendment filed 3/12/04 is acknowledged and has been entered.

3. Applicant is reminded of Applicant's election without traverse of Group I (claims 1-27), and species of the specific complex of a TCR tetramer comprising four $\alpha\beta$ dimers and the specific linker molecule of avidin in Paper No. 7.

Claims 1-11, 14-27 and 34-36 read on the elected species and are presently being examined.

4. The disclosure is objected to because of the following informality:

There is a spelling error on page 93 of Appendix B filed 7/25/03 (marked-up copy of the substitute specification) and on page 80 of Appendix A filed 7/25/03 (the clean copy of the substitute specification), i.e., "R frenc s". In addition, page 92 of Appendix A appears to have irrelevant information on page 92 or on page 105 of Appendix B, i.e., a header and 5i, and there appears to be extra page at 106 in Appendix B that is a "document comparison done by Deltaview".

Appropriate correction is required.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4, 10, 11, 17 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Gregoire et al (PNAS USA 1991, 88: 8077-8081).

Gregoire et al teach multimers of chimeric soluble TCR- $\alpha\beta$ heterodimers linked to Ig C κ or to Ig CH₁, CH₂ or CH₃ (last paragraph on page 8081). Gregoire et al teach that the alpha chain consists of the TCR V α region joined to the first exon of TCR C α and the C region of the Ig κ light chain, and the beta chain consists of the TCR V β region joined to the first exon of TCR V β and the C region of the Ig κ light (page 8078, second column at the last paragraph, figure 1 and figure 4 and Materials and Methods section). Gregoire et al teach that for multimers, one of the Ig κ regions is replaced with Ig CH₁, CH₂ or CH₃ (last paragraph on page

Art Unit: 1644

8081). Gregoire et al teach that the chimeric polypeptides do not include the second exon of TCR C α and C β gene, and therefore lack the cysteine residues normally involved in the covalent linkage of the TCR α and TCR β chains (page 8080, first column at lines 2-6). Gregoire et al teach that the ability of their constructs to form heterodimers may be due to the lack of the cysteine residue located at the COOH-terminal to the C α and C β regions (page 8080 at the second column, first paragraph). Gregoire et al teach that an illegitimate interaction between the COOH terminus of a TCR C domain and the NH₂ terminus of a C κ domain may distort the proper pairing of the C κ domains and accordingly their ability to be disulfide linked, i.e., the C κ domains dimerize with each other, and that they associated as noncovalent dimers (page 8080 at the first column and last 8 lines bridging second column and page 8081, last paragraph, first sentence). Gregoire et al teach their TCR in a pharmaceutically acceptable formulation (page 8078, second column at the third full paragraph). With regard to the recitation of refolded recombinant TCR in claims 1 and 11, Gregoire et al teach 3 mAb epitopes on V α and V β that are recognized on both their constructs as well as surface expressed TCR, that their constructs react with an anti-clonotypic antibody and two antibodies directed to the C domain of the TCR α and β chains, and that the soluble TCR molecules are folded in a conformation indistinguishable from that which they assume at the cell surface (Abstract and page 8081, first paragraph). Thus the chimeric soluble TCR multimers taught by Gregoire et al appears to be the same as the claimed synthetic multivalent TCR. With regard to instant claim 17, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103^c and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 1644

8. Claims 1-11, 14-18, 26, 27 and 34-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Schatz (Biotechnology, 11, 1993, pages 1138-1143, Applicant's IDS reference in the Form 1449 filed 11/5/99).

WO 97/35991 teaches soluble (i.e., extracellular domains) recombinant divalent and multivalent analogs (including tetravalent, i.e., a tetramer) of heterodimeric proteins and pharmaceutical compositions thereof, including $\alpha\beta$ TCR that possess enhanced affinity for their target molecules, said $\alpha\beta$ TCRs being associated via Ig linker molecules which may further comprise a toxin, i.e., a "cytotoxic agent" as recited in instant claim 26, and/or may be further linked by association via avidin (especially page 8, line 31, page 9, lines 1-4, page 10, lines 27-31, page 11, lines 1-7, page 14, lines 7-16, Figure 1D and legend, claims 1-5, 8, 10-14, 17, 27 and 28, page 1, lines 14-17, page 16, lines 1-14). With regard to instant claim 17, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1). WO 97/35991 also teaches production of the multimers in baculovirus with a yield of about 1 ug/ml (i.e., about 1 mg/L). WO 97/35991 also teaches short flexible Gly-Ser spacers between the TCR chain and the Ig portion (Figure 1D and legend).

WO 97/35991 does not teach multivalent soluble $\alpha\beta$ TCR wherein each chain has a heterologous C-terminal dimerisation peptide which is a coiled coil domain (such as a leucine zipper from c-fos and c-jun) dimerization peptide, which dimerize, one with the other, and wherein a short flexible linker is between the TCR and the dimerisation domain, and further, wherein a disulfide bond present in the native TCR between the α and β chains adjacent to the cytoplasmic domain is absent from the recombinant TCR. WO 97/35991 does not teach the TCR complex of instant claims, wherein the disulfide bond between the α and β chain of the TCR are absent.

Golden et al teach soluble heterodimeric TCR comprising an α and a β chain, each chain comprising a leucine zipper which dimerizes, one with the other, produced in E. coli at yields of 4-5 mg/L (especially Abstract).

O'Shea et al teach heterodimer formation through leucine zippers from c-fos and c-jun (especially Abstract).

Art Unit: 1644

Garbozci et al teach a soluble TCR without the interchain disulfide bond present in native TCRs, and that the heterodimerization, refolding and antigenic specificity of the TCR do not require its interchain disulfide bond, transmembrane segments or glycosylation (especially Abstract and page 5408, column 1). Garbozci et al further teach that when α and β chains expressed without the cysteines that form the interchain disulfide bond were refolded together, they formed heterodimers spontaneously and at higher yields. Garbozci et al teach the yield is routinely 100 mg/ml and the refolded noncovalently associated TCR is stable and very soluble and displays little or no aggregation upon long term storage at 4 degrees C (especially page 5404, column 1, lines 1-14 and page 5407, column 1 at lines 19-22).

Schatz teaches a biotin holoenzyme synthetase encoded by birA, useful for labeling, purification, detection and immobilization of proteins. Schatz teaches fusion proteins comprising polypeptides and the birA sequence for biotinylation at a single specific site (especially abstract and last 2 paragraphs). Schatz teaches biotinylation of a variety of molecules is of practical importance, primarily due to the very tight binding of biotin to the proteins avidin and streptavidin, and that it is advantageous to accomplish biotinylation at a single site using an agent with site specificity (especially paragraph spanning columns 1 and 2 on page 1138).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the soluble heterodimeric TCR of Golden et al, with the Gly-Ser linker of WO 97/35991, as the monomeric TCR in the multimers of WO 97/35991 that were multimerized by avidin and to have produced the proteins in E. coli as taught by Golden et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made to have used any leucine zipper of appropriate stability such as the leucine zippers from c-fos and c-jun taught by O'Shea et al in the soluble heterodimeric TCR of Golden et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have to have a recombinant TCR as taught by the combination of WO 97/35991 and Golden et al without the disulfide bond, as taught by Garbozci et al and further modified as taught by Schatz.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the yield of correctly folded soluble TCR of WO 97/35991 as modified with leucine zippers as taught by Golden et al and O'Shea et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Garbozci et al teach that the presence of said bond is not important for heterodimerization and refolding, and further in order to facilitate the production of soluble correctly associated TCR, i.e., in order to insure that disulfide bonds did not form between homologous chains or with other contaminating proteins during purification.

With regard to instant claims 9 and 18, one of ordinary skill in the art at the time the invention was made would have been aware that biotin is the binding partner for avidin, and that biotin would have been incorporated into the monomer TCR in order that the monomer TCR could

Art Unit: 1644

have been linked via avidin to form multimers and as taught by Schatz. With regard to instant claim 18, one of ordinary skill in the art at the time the invention was made would have been aware that the C-terminus of the heterodimer chain would be the optimal location for biotinylation, rather than at the N-terminus where preservation of antigen binding function was paramount.

Applicant's arguments in the amendment filed 3/12/04 have been fully considered, but are not persuasive.

It is Applicant's position is of record in the said amendment on pages 8-12, and is based on an assertion that upon reading of Golden et al and Garboczi et al one of ordinary skill in the art would not find any teaching, motivation or expectation of success to arrive at Applicant's claimed invention.

It is the Examiner's position with regard to Applicant's arguments about Garboczi et al in the paragraph spanning pages 9 and 10 of Applicant's said amendment, that although the calculated molecular mass of the heterodimer is 50.2 kDa, shape affects the mobility of a molecule through a sieving gel, thus all the molecules in one gel must have similar shapes for valid comparison, and the elution of a complex from a sieving gel in the 40kDa fraction was able to bind MHC/peptide with specificity. It is the Examiner's further position that the final office action mailed 12/19/03 did not suggest that Figure 4 relates to a native gel. It is the Examiner's position that Garboczi et al teach on page 5409 at the paragraph spanning columns 1 and 2, that if in the absence of the interchain disulfide bond, low affinities between some pairings of the alpha and beta chains should limit heterodimer stability, high concentrations of the polypeptides now available from bacterial expression could be used to overcome this. Garboczi et al teach on page 5404 at the first full paragraph the advantage of expressing alpha and beta chains without the cysteines that form the interchain disulfide bond when expressing and/or refolding together the two said chains. Applicant states in the said amendment on page 9 "The SDS in this gel is, of course, expected to denature the TCR alpha and beta chains", referring to an SDS-PAGE gel. Golden et al teach improvement in yield of co-expressed alpha and beta chain of a murine TCR, different from the human TCR produced by Garboczi et al, by creation of leucine zipper fusion alpha and beta sequences. The yield taught by Golden et al in E. coli is 20X lower than the yield taught by Garboczi et al in E. coli. Regarding Applicant's comments about Golden et al teaching away from the present invention with regard to exclusion of the interchain disulfide bonded forming cysteines, Applicant states in the said amendment on page 9 with regard to SDS-PAGE gel analysis, that "The SDS in this gel...is expected to denature TCR alpha and beta chains [and gels that are not native gels such as the one referred to by Applicant in Golden et al] provides no assistance in answering the question of the non-covalent association of the TCR chains under native conditions, one way or another."

Art Unit: 1644

9. Claims 24 and 25 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Schatz (Biotechnology, 11, 1993, pages 1138-1143, Applicant's IDS reference in the Form 1449 filed 11/5/99) as applied to claims 1-11, 14-18, 26, 27 and 34-36 supra and further in view of U.S. Patent No. 5,635,363 (Applicant's IDS reference in Form 1449 filed 11/5/99).

WO 97/35991, Golden et al, O'Shea et al, Garboczi et al and Schatz (i.e., "the combined references") have been discussed supra. In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1).

The combined references do not teach a multimeric TCR complex comprising a "detectable label" recited in instant claim 25, nor attached to a "solid structure" recited in instant claim 24.

U.S. Patent No. 5,635,363 discloses soluble MHC/peptide tetramers which are biotinylated and multimerized with streptavidin or with avidin and which further comprise a light detectable label FITC or an enzyme (especially claims) and which further may be bound to an insoluble support such as a bead, i.e., a "solid structure", for the purpose of assay (especially column 8, lines 4-16).

It would have been prima facie obvious to one of ordinary skill at the time the invention was made to have biotinylated, as disclosed by the '363 patent for soluble MHC/peptide tetramers, the soluble TCR complexes taught by the combined references and to have multimerized them using avidin, and further to have labeled them with a detectable label such as is disclosed by the '363 patent for the MHC/peptide tetramers, or to have bound them to a bead, i.e., a solid structure.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to form more avid multimers because the combined references teach the claimed TCR complexes, WO 97/35991 teaches multimers and tetramers and both WO 97/35991 and the '363 patent teach use of avidin for multimerization of heterodimeric proteins, and also because one of ordinary skill in the art at the time the invention was made would have been motivated to facilitate detection because WO 97/35991 teaches that multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses.

Art Unit: 1644

Applicant's arguments in the amendment filed 3/12/04 have been fully considered, but are not persuasive.

Applicant's arguments and Examiner's position supra with regard to item #6 of this Office Action, apply herein.

10. Claims 1 and 19-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and further in view of Ahmad et al (Cancer Res., Volume 53: 1484-1488, 1993).

WO 97/35991, Golden et al, O'Shea et al and Garboczi et al (i.e., "the combined references") have been discussed supra. The combined references do not teach a multimeric TCR complex attached to a lipid vesicle via derivatised lipid components of the vesicle.

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective in vivo drug delivery.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have attached the multimeric TCR complex taught by the combined references to the liposome of Ahmad et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver in vivo the multimeric TCR complex taught by the combined references, including WO 97/35991 to be useful for in vivo therapy. Claim 23 is included in this rejection because it would also have been prima facie obvious to embed the TCR complex in the liposome of Ahmad et al because Ahmad et al teach effective delivery of a substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome (especially Abstract). Instant claim 24 is included in this rejection because the claim limitation "solid structure" can read on "liposome" of the art reference.

Applicant's arguments in the amendment filed 3/12/04 have been fully considered, but are not persuasive.

Applicant's arguments and Examiner's position supra with regard to item #6 of this Office Action, apply herein.

Art Unit: 1644

11. Claims 1-11, 14-18, 24-27, and 34-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chang et al (PNAS USA 1994, 91: 11408-11412, IDS reference) in view of Gregoire et al (PNAS USA 1991, 88: 8077-8081), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99), Wulfing (J. Mol. Biol. 1994, 242: 655-669), U.S. Patent No. 5,643,731 and U.S. Patent No. 5,582,996.

Chang et al teach a soluble TCR in which the TCR alpha and beta V and C extracellular segments are fused at the carboxy terminal end to 30 amino acid long segments via a cleavable flexible linker (Abstract and figure 2). Chang et al teach that the peptide segments have been previously shown to selectively associate to form stable heterodimeric coiled coil, the leucine zipper (Abstract and page 11408 at the second column, first three lines of the second paragraph). Chang et al teach that the disulfide linked $\alpha\beta$ heterodimer is the clonally unique component that possesses a recognition site for antigen in the context of the MHC (page 11408, at the first column, first paragraph after Abstract). Chang et al teach that the structure of the heterodimeric TCR protein is judged to be native when probed with a panel of 17 mAbs specific for the alpha and beta C and V domains (Abstract and page 11411 at the last paragraph bridging the page with page 11412). Chang et al further teach facilitation of association of any type of naturally occurring heterodimeric structure, and that association between individual protein domains, such as TCR $V\alpha$ and $V\beta$ can be fostered in the absence of other protein segments ($C\alpha$ and $C\beta$) (page 11412, at the second column).

Chang et al do not teach that a disulfide bond present in native TCRs between the alpha and beta chain is absent in the recombinant TCR having both the alpha and beta variable and constant region domains, nor do Chang et al teach that the heterodimers are present as multivalent TCR complexes.

Gregoire et al teach multimers of chimeric soluble TCR- $\alpha\beta$ heterodimers linked to Ig C κ or to Ig CH₁, CH₂ or CH₃ (last paragraph on page 8081). Gregoire et al teach that the alpha chain consists of the TCR $V\alpha$ region joined to the first exon of TCR $C\alpha$ and the C region of the Ig κ light chain, and the beta chain consists of the TCR $V\beta$ region joined to the first exon of TCR $V\beta$ and the C region of the Ig κ light chain and the constructs expressed in E. coli (page 8078, second column at the last paragraph, figure 1 and figure 4 and Materials and Methods section). Gregoire et al teach that for multimers, one of the Ig κ regions is replaced with Ig CH₁, CH₂ or CH₃ (last paragraph on page 8081). Gregoire et al teach that the chimeric polypeptides do not include the second exon of TCR $C\alpha$ and $C\beta$ gene, and therefore lack the cysteine residues normally involved in the covalent linkage of the TCR α and TCR β chains (page 8080, first column at lines 2-6). Gregoire et al teach that the ability of their constructs to form heterodimers may be due to the lack of the cysteine residue located at the COOH-terminal to the $C\alpha$ and $C\beta$ regions (page 8080 at the second column, first paragraph). Gregoire et al teach that an illegitimate interaction between the COOH terminus of a TCR C domain and the NH₂ terminus of a C κ domain may distort the proper pairing of the C κ domains and accordingly their ability to be disulfide linked, i.e., the C κ domains dimerize with

Art Unit: 1644

each other, and that they associated as noncovalent dimers (page 8080 at the first column and last 8 lines bridging second column and page 8081, last paragraph, first sentence). Gregoire et al teach their TCR in a pharmaceutically acceptable formulation (page 8078, second column at the third full paragraph). With regard to the recitation of refolded recombinant TCR in claims 1 and 11, Gregoire et al teach 3 mAb epitopes on V α and V β that are recognized on both their constructs as well as surface expressed TCR, that their constructs react with an anti-clonotypic antibody and two antibodies directed to the C domain of the TCR α and β chains, and that the soluble TCR molecules are folded in a conformation indistinguishable from that which they assume at the cell surface (Abstract and page 8081, first paragraph).

It is clear from figure 2 on page 11410 in the teaching of Chang et al, and from the teaching of Gregoire et al that without the C domains, a conjugate of TCR V α and V β taught by Chang et al would not have the interchain disulfide bond because the cysteines that form the interchain disulfide is not found in the TCR V α and V β . Furthermore, from the teaching of Gregoire et al, one of ordinary skill in the art would have expected that the lack of the disulfide bond located at the COOH terminal end of the C α and C β regions facilitates the pairing of the dimerizing Ig C κ or C λ .

Garbozci et al teach a soluble TCR without the interchain disulfide bond present in native TCRs, and that the heterodimerization, refolding and antigenic specificity of the TCR do not require its interchain disulfide bond, transmembrane segments or glycosylation (especially Abstract and page 5408, column 1). Garbozci et al further teach that when α and β chains expressed without the cysteines that form the interchain disulfide bond were refolded together, they formed heterodimers spontaneously and at higher yields. Garbozci et al teach the yield is routinely 100 mg/ml and the refolded noncovalently associated TCR is stable and very soluble and displays little or no aggregation upon long term storage at 4 degrees C and binds specifically to the ligand HLA-A2/Tax (especially page 5404, column 1, lines 1-14, page 5406, second column at the last two paragraphs and page 5407, column 1 at lines 19-22).

Wulfing et al teach that the TCR fragments are correctly folded in the periplasm of E. coli. Wulfing et al teach that the correctly folded TCR is essentially stable, whereas misfolded TCR is rapidly degraded, and that the effect of increased yields in the direct over-expression system is due to enhanced in vivo folding, working synergistically with substantially higher intrinsic proteolytic stability of the correctly folded material (page 665, second column at the last two paragraphs, and that bridging page 666). Wulfing et al teach that to overcome the low affinity of TCR, T cells simultaneously use multiple TCRs to increase the avidity of recognition (last paragraph on page 795).

Art Unit: 1644

From the teaching of Wulfing et al, one of ordinary skill in the art at the time the invention was made would have expected that higher yields of TCRs are correlated with correct TCR folding, and thus a decrease in the yield of alpha and beta chains of TCR expressed with the interchain disulfide bonds, as compared to alpha and beta chains of TCR expressed without the interchain disulfide bonds as taught by Garboczi et al, indicates an increase in misfolding of alpha and beta chains of TCR expressed with the interchain disulfide bonds, i.e., that the interchain disulfide bond appears to interfere with the folding of the alpha and beta chains of TCRs.

Therefore, from the teaching of Garboczi et al and Wulfing et al, one of ordinary skill in the art at the time the invention was made would have expected that the interchain disulfide bond of TCR not only is not necessary for TCR binding to the target peptide, but that it could also interfere with the folding of the alpha and beta chains, resulting in lower yield.

U.S. Patent No. 5,643,731 discloses that c-jun and v-fos are particularly the preferred leucine zipper peptides (column 3 at lines 38-42). U.S. Patent No. 5,643,731 further discloses that the leucine zipper peptides can be linked via a flexible linker to antigen receptor molecules, i.e., such as TCR or antibody, and multimerized via a carrier molecule that is a multivalent attachment molecule, and further that the constructs can be attached to solid supports (especially Abstract and Figures). U.S. Patent No. 5,643,731 discloses that the antigen receptor molecule-leucine zipper peptides can comprise a detectable label or a cytokine, i.e., an immunostimulating agent or enzymes, i.e., protein tags, or other fusion proteins and also to streptavidin or biotin (especially Figures and column 4 at lines 30-36 and column 2).

U.S. Patent No. 5,582,996 discloses that dimeric Fab is formed when a Fab with a c-fos leucine zipper is mixed with a Fab with a c-jun leucine zipper. U.S. Patent No. 5,582,996 further discloses that the hinge region of the dimeric Fab retains sufficient flexibility to permit the Fab fragments to bind antigen in a manner similar to that of normal antibodies (especially Example 7 at columns 15-16).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have: combined the teaching of Chang et al that the association between individual protein domains such as TCR V α and V β can be fostered in the absence of protein segments such as C α and C β and use of coil coiled domains such as those that form leucine zippers linked to the said V α and V β via linkers, the teaching of Gregoire et al that lack of the of the disulfide bond located at the COOH terminal end of C α and C β facilitates pairing of the dimerizing construct and that multivalency is advantageous, the teaching of Garboczi et al that the interchain disulfide bond of TCR is not necessary for its binding to the target peptide/MHC and that it can interfere with folding of the alpha and beta chains, thus resulting in lower yield, and the latter also taught by Wulfing et al, for making a chimeric TCR taught by Chang et al, wherein the interchain disulfide bond between the alpha and beta chains is omitted and to have multimerized the soluble heterodimers for increased valency as taught by Gregoire et al and because Wulfing et al teach low affinity of TCR and need to

Art Unit: 1644

increase the avidity for recognition using multiple TCRs (for cell surface TCR heterodimers), including as dimers, trimers or tetramers, in light of the disclosure of U.S. Patent No. 5,582,996 that leucine zipper peptides linked via a flexible linker to antigen receptor molecules can be multimerized via a carrier molecule that is a multivalent attachment molecule and/or can be linked to solid supports and in light of the disclosure of U.S. Patent No. 5,582,996 that c-jun and v-fos are particularly the preferred leucine zipper peptides and that of U.S. Patent No. 5,582,996 that a dimeric antigen receptor molecule is formed when a component of said molecule with a c-fos leucine zipper is mixed with another component with a c-jun leucine zipper. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have coupled or fused the construct to a solid support, or to a cytokine or to an enzyme or to biotin as disclosed for the antigen receptor molecule multimers disclosed by U.S. Patent No. 5,643,731. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the multimer in a composition with a pharmaceutically acceptable carrier since their TCR in a pharmaceutically acceptable formulation since Gregoire et al teach their TCR in a pharmaceutical composition. It would have been obvious to biotinylate the TCR complexes at the C-terminus because one of ordinary skill in the art would have expected that the C-terminus is not the site where the recognition of antigen takes place and would be least likely to interfere with antigen binding as compared to biotinylation at the N-terminus.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a multimeric TCR complex of higher avidity and in higher yield.

With regard to instant claim 17, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

12. Claims 19-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chang et al (PNAS USA 1994, 91: 11408-11412, IDS reference) in view of Gregoire et al (PNAS USA 1991, 88: 8077-8081), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99), Wulfing (J. Mol. Biol. 1994, 242: 655-669), U.S. Patent No. 5,643,731 and U.S. Patent No. 5,582,996 as applied to claims 1-11, 14-18, 24-27, and 34-36 above, and further in view of Ahmad et al (Cancer Res. 1993, 53: 1484-1488, of record).

The teaching of Chang et al, Gregoire et al, Garboczi et al, Wulfing et al, U.S. Patent No. 5,643,731 and U.S. Patent No. 5,582,996 have been set forth above, hereafter "the combined references".

The combined references do not teach wherein the multimeric TCR complex is attached to a lipid vesicle via derivatized lipid components of the vesicle.

Art Unit: 1644

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective in vivo drug delivery.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have attached the multimeric TCR complex taught by the combined references to the liposome of Ahmad et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver in vivo the multimeric TCR complex taught by the combined references, to be useful for in vivo administration, since Ahmad et al teach enhancement of in vivo delivery an antigen receptor using liposomes and Gregoire et al teach pharmaceutical compositions comprising another antigen receptor, TCR. Claim 23 is included in this rejection because it would also have been prima facie obvious to embed the TCR complex in the liposome of Ahmad et al because Ahmad et al teach effective delivery of a substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome (especially Abstract). Instant claim 24 is also included in this rejection because the claim limitation "solid structure" can read on "liposome" of the art reference.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Art Unit: 1644

14. Claims 1-11, 14-27 and 34-36 are provisionally rejected under the judicially created doctrine of double patenting over claims 22-34 of copending Application No. 10/014,326 in view of WO 97/35991, Ahmad et al and U.S. Patent No. 5,643,731. This is a provisional double patenting rejection.

The instant claims are drawn to a multivalent TCR, whereas the claims of Application No. 10/014,326 are drawn to a heterodimeric monovalent TCR.

WO 97/35991 teaches soluble (i.e., extracellular domains) recombinant divalent and multivalent analogs (including tetravalent, i.e., a tetramer) of heterodimeric proteins and pharmaceutical compositions thereof, including $\alpha\beta$ TCR that possess enhanced affinity for their target molecules, said $\alpha\beta$ TCRs being associated via Ig linker molecules which may further comprise a toxin, i.e., a "cytotoxic agent" as recited in instant claim 26, and/or may be further linked by association via avidin (especially page 8, line 31, page 9, lines 1-4, page 10, lines 27-31, page 11, lines 1-7, page 14, lines 7-16, Figure 1D and legend, claims 1-5, 8, 10-14, 17, 27 and 28, page 1, lines 14-17, page 16, lines 1-14). In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1). WO 97/35991 also teaches production of the multimers in baculovirus with a yield of about 1 ug/ml (i.e., about 1 mg/L). WO 97/35991 also teaches short flexible Gly-Ser spacers between the TCR chain and the Ig portion (Figure 1D and legend).

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective in vivo drug delivery.

U.S. Patent No. 5,643,731 discloses that c-jun and v-fos are particularly the preferred leucine zipper peptides (column 3 at lines 38-42). U.S. Patent No. 5,643,731 further discloses that the leucine zipper peptides can be linked via a flexible linker to antigen receptor molecules, i.e., such as TCR or antibody, and multimerized via a carrier molecule that is a multivalent attachment molecule, and further that the constructs can be attached to solid supports (especially Abstract and Figures). U.S. Patent No. 5,643,731 discloses that the antigen receptor molecule-leucine zipper peptides can comprise a detectable label or a cytokine, i.e., an immunostimulating agent or enzymes, i.e., protein tags, or other fusion proteins and also to streptavidin or biotin (especially Figures and column 4 at lines 30-36 and column 2).

Art Unit: 1644

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed multimers of the heterodimeric monovalent TCR of Application No. 10/014,326 given the teaching of WO 97/35991 and U.S. Patent No. 5,643,731 and to have attached the multimeric TCR complexes to the liposome taught by Ahmad et al.

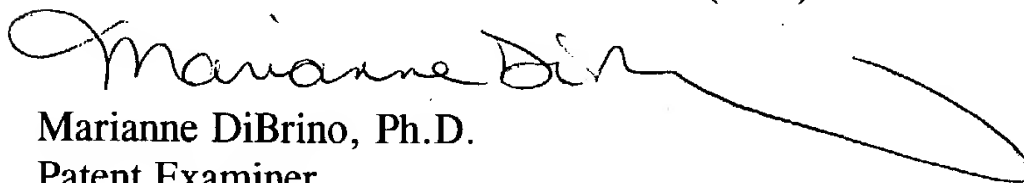
One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to construct higher avidity TCR/composition thereof comprising a pharmaceutically acceptable formulation because WO 97/35991 teaches TCR multimers have enhanced affinity and Ahmad et al teach enhanced in vivo drug delivery for another type of antigen receptor using liposomes and U.S. Patent No. 5,643,731 discloses heterodimerized α or β TCR chains with leucine zippers, and attachment to labels or cytokines or biotin or streptavidin. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver the multimeric TCR complex in vivo. Instant claim 23 is included in this rejection because it would also have been prima facie obvious to embed the TCR complex in the liposome because Ahmad et al teach effective delivery of a substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome.

Instant claim 24 is included in this rejection because the claim limitation "solid structure" can read upon liposome. With regard to the recitation of "therapeutic agent" in claim 33 of Application No. 10/014,326, claim 26 of the instant application recites "cytotoxic agent or an immunostimulating agent", i.e., a "therapeutic agent". Although instant claim 8 recites "fusion protein comprising an amino acid sequence encoding a protein tag", the teaching of WO 97/35991 is for a toxin, that toxin potentially being a protein. Claims 23-25 of Application No. 10/014,326 recite wherein said TCR is stable at low concentrations, a concentration of about 20 mg/ml, or a concentration below 1 mg/ml, respectively. Although the references do not teach the TCR is stable at the recited concentrations, the claimed multimeric TCR appears to be the same as that recited in claims 23-25 of Application No. 10/014,326. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of Application No. 10/014,326 does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on Applicant to prove that the claimed product is different from that recited in Application No. 10/014,326 and to establish patentable differences. See *In re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Art Unit: 1644

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



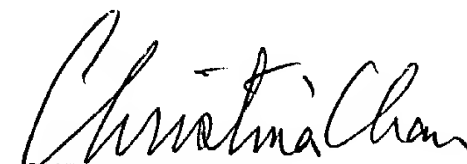
Marianne DiBrino, Ph.D.

Patent Examiner

Group 1640

Technology Center 1600

October 6, 2004



CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600